REMARKS/ARGUMENTS

Claims 1-25 are pending in this application and stand rejected on various grounds. In particular, the rejection under 35 U.S.C. §112, first paragraph, for alleged lack of adequate written description has been maintained from earlier Office Actions. In addition, all claims have been rejected under 35 U.S.C. §103 as allegedly obvious over Hart *et al.*, BIO/TECHNOLOGY Vol. 12, November 1994 in view of Wetzel *et al.* (EP 0155189), alone or in combination with additional references.

All rejections are respectfully traversed, for reasons detailed below.

Claim Rejections - 35 U.S.C. §112, First Paragraph

Claims 1-25 remain rejected under 35 U.S.C. §112, first paragraph, for alleged lack of adequate written description for the claimed subject matter. According to the rejection, Applicants' prior arguments that the identity of a particular nucleic acid encoding either a lysozyme or a polypeptide and the promoter is not essential to the claimed invention are not persuasive.

In support of the rejection, the Examiner heavily relies on The Regents of the University of California v. Eli Lilly, 119 F.3d 1559, 43 U.S.P.Q 2d 1398 (Fed. Cir. 1997), and the interpretation of Eli Lilly in the Guidelines for Examination of Patent Applications Under the 35 U.S.C. §112, Sec. 1, "Written Description Requirement" (January 5, 2001) 66 FR 1099 (hereinafter referred to as the "Final Written Description Guidelines"). It is submitted that the Examiner misinterprets both the CAFC's holding in Eli Lilly and the final Written Examination Guidelines' application of Eli Lilly.

In Eli Lilly, the Federal Circuit held that a disclosure of the cDNA for rat insulin did not allow the applicant to receive patent protection for cDNA encoding mammalian, vertebrate, or human insulin. Citing Fiers v. Revel, 984 F.2d 1164, 1171, 25 USPQ2d 1601, 1606 (Fed. Cir. 1993), the Federal Circuit stated that an adequate written description of genetic material "requires a precise definition, such as by structure, formula, chemical name, or physical properties." (Emphasis added.) "A description of a genus of cDNAs may be achieved by means of a recitation of a representative number of cDNAs, defined by nucleotide sequences, falling

within the scope of the genus or a recitation of structural features to the members of the genus, which features constitute a substantial portion of the genus." Eli Lilly, 119 F.3d at 1569, 43 USPQ2d at 1406.

While the holding of Eli Lilly and its progeny has later been expanded to assessing the written description for proteins as well, it is clear that the extent of detail in the specification's teaching that is needed to meet the written description requirement of 35 U.S.C. §112 varies with the nature of the invention.

The Examiner's attention is specifically directed to the Federal Circuit's recent decision in Capon v. Eshhar v. Dudas (418 F.3d 1349: 2005 (U.S. App); 76 USPQ (BNA) 1078) where the Federal Circuit held that the disclosure of a complete nucleotide sequence is not required to meet to written description requirement when a chimeric gene is claimed. In Capon, the USPTO's Board of Patent Appeals and Interferences (the Board) rejected a claim to a chimeric DNA invention under the test of Eli Lilly, finding that "the parties' claim is not described in their specifications . . . by reference to . . . the structure, formula, chemical name, or physical properties of many protein domains." Capon, 418 F.3d at 1355.

In explaining its ruling overturning the Board's decision, the Federal Circuit reaffirmed that "[t]he 'written description' requirement implements the principle that a patent must describe the technology that is sought to be patented." The Court added, however that:

> *The descriptive text needed to meet [the written description requirement] varies with the nature and scope of the invention at issue, and with the scientific and technologic knowledge already in existence. The law must be applied to each invention that enters the patent process, for each patented advance is novel in relation to the state of the science. . . [T]he law . . . will vary with differences in the state of the knowledge in the field and differences in the predictability of the science.*

Ibid, at 1357.

The Federal Circuit went on to clarify:

> *The "written description" requirement states that the patentee must describe the invention; it does not state that every invention must be described the same way.*

Ibid, at 1358.

As the Federal Circuit properly recognized, one size does not fit all. The written description standard, like other indicia of patentability, must be examined in a fact-specific manner, taking into account the nature of the invention and the state of the art.

Applying the Capon standard to the present application it is clear that the specification of the present application need not disclose the sequences of phage lysozymes, plasmids, promoters, and the like, in order to meet the written description requirement of 35 U.S.C. §112, first paragraph, for the claimed invention. Phage lysozymes that facilitate the lysis of phage-infected bacterial cells were well known in the art at the time the present invention was made. As stated on page 13, lines 5-7 of the specification, the "lysozyme may be from any bacteriophage source, including T7, T4, lambda, and mu bacteriophages." References establishing the availability of the T4 lysozyme are provided at page 13, lines 8-20. Lysozymes from other bacteriophages, such as phages T7, T3 and T5, were also known in the art at or before the priority date of this application, and disclosed, for example, in DeMartici et al., J Virology 18:459-461 (1975) (T3 and T5) and Jerozalmi and Steitz EMBO J. 17:4101-4112 (1999) (T7). Copies of these documents were submitted for the Examiner's consideration with Applicants' response of August 10, 2004. Inducible promoters are defined at page 14, lines 17-19, and specific inducible promoters are listed, along with references for their availability, at page 22, lines 1-27. Similarly, expression plasmids were well known as early as in 1977 (pBR322, see page 20, line 22 – page 21, line 30 of the specification). Methods for analysis to confirm the correct sequences in various plasmids constructed to perform the methods claimed in the present application were also known, as described in the references cited on page 23, lines 6-14 of the specification. Finally, the coding sequences and the encoded amino acid sequences of a plethora of mammalian proteins were well known in the art at the priority date of this application, including the proteins listed at page 15, line 23 – page 16, line 32 of the specification.

Just as in Capon, when assessing compliance with the written description requirement, the law must take cognizance of these scientific facts. None of the CAFC decisions addressing the issue of written description, including Eli Lilly, require re-description of what was already known. As the Capon court noted:

When the prior art includes the nucleotide information, precedent does not set a per se rule that the information must be determined afresh.

Capon at 1358.

Since the invention claimed in the present application is not in discovering DNA sequences, but in the use of such sequences in a novel and unobvious method, the Examiner erred in finding that the specification does not meet the written description requirement. There is no requirement that the specification reiterate the sequences of a variety of known polypeptides, phage lysozymes, promoters, or expression vectors that can be used in the claimed methods, and in fact for brevity's sake such information already known in the art would not be expected to be included.

Applicants submit that one of ordinary skill at the time the present invention was made would have reasonably accepted that Applicants were in the possession of the genera of nucleic acids encoding the heterologous polypeptides and phage lysozymes, the sequences of expression vectors, including inducible promoters and promoters with low basal expression, required to practice the claimed invention within the full scope of the claims currently pending. Accordingly, the reconsideration and withdrawal of the present rejection is respectfully requested.

Claim Rejections - 35 U.S.C. §103

1. Claims 1-7, and 9-24 were rejected as allegedly obvious over Hart *et al.* (BIO/TECHNOLOGY Vol. 12, November 1994) in view of Wetzel *et al.* (EP 0155189). Hart *et al.* was cited for its disclosure of a process for large-scale production of IGF-I from the periplasm of *E. coli* by culturing *E. coli* host cells having a plasmid comprising an inducible promoter and nucleic acid encoding a signal sequence for secretion into the periplasm linked to human IGF-I. Wetzel *et al.* was cited for its teaching of a plasmid comprising an inducible promoter and nucleic acid encoding a T4 phage lysozyme.

According to the rejection, it "would have been obvious to one of ordinary skill in the art at the time the invention was made to modify the method of Hart *et al.* such that the *E. coli* host cell is further transformed with the plasmid vector of Wetzel *et al.*, the host cells are

mechanically disrupted to release the IGF-I from the periplasm, and the IGF-I is recovered in the presence of EDTA." The Examiner adds that a motivation to combine existed "in order to have synthesis of lysozyme which ruptures the polysaccharide membrane of the *E. coli* host cell and simplifies the purification of the human IGF-I." Finally, according to the rejection "it would have been obvious to one of ordinary skill in the art to construct a vector having the nucleic acid encoding the T4 lysozyme and nucleic acid encoding human IGF-I on the same vector for the purposes of having a [sic] only a single vector which simplifies transformation of the *E. coli* host cell." Based on these conclusory statements, the Examiner finds that, at the time the invention was made, the claimed invention "was as a whole clearly *prima facie* obvious."

Applicants respectfully disagree, and vigorously traverse the rejection.

Hart *et al.* describe a 10-kiloliter-scale process for recovery of periplasmic IGF-I polypeptide from *E. coli*. High level expression of human IGF-I with a lamB signal sequence in *E. coli* led to accumulation of periplasmic refractile bodies (page 1113, second column). First, the authors attempted the typical isolation procedure involving a mechanical cell breakage step followed by a centrifugation step to recover the protein from the refractile bodies. The results were disappointing in that almost 40% of the total product was lost to the supernatant after three passes through the Gaulin homogenizer (see the results shown in Table 1 of the paper). In order to enhance recovery yield, a new procedure, including *in situ* solubilization by a chaotrope and a reductant, and two-phase extraction involving the addition of a polymer and salt to the solubilization mixture, was developed. At the end of the abstract, the authors state that together, "the techniques of *in situ* solubilization and aqueous two-phase extraction provide a new, high yield approach for isolating recombinant protein which is accumulated in more than one form during fermentation."

Wetzel *et al.* (EP 0 155 189) disclose a method to induce a recombinant cell culture to produce lysozymes without killing the bacterial host cells.

There is no motivation to combine Hart et al. and Wetzel et al.

Contrary to the Examiner's opinion, there is no motivation to combine Hart *et al.* and Wetzel *et al.* According to Hart *et al.*, combined use of the *in situ* solubilization technique and

aqueous two-phase extraction achieved the desired result by providing a high yield approach for the isolation of IGF-I and potentially other non-native proteins from cellular biomass. In view of this, Hart *et al.* had no motivation whatsoever to look for other approaches for isolating periplasmic IGF-I from *E. coli*. Thus, Hart *et al.* would not have been motivated to use a phage lysozyme under the control of a promoter with low basal expression or of an inducible promoter in order to recover IGF-I or any other heterologous protein originally accumulated in the form of refractile particles in the bacterial periplasm, as instantly claimed.

Even if Hart et al. and Wetzel et al. were properly combined, they would still not make obvious the invention claimed in the present application.

Assuming arguendo that Hart *et al.* and Wetzel *et al.* could be properly combined, the combination would result in a complicated method, including the expression of a phage lysozyme along with the expression of heterologous protein, such as IGF-I, followed by *in situ* solubilization and aqueous two-phase extraction steps. There is nothing in either Hart *et al.* or in Wetzel *et al.* that would suggest that the co-expression of the protein and phage lysozyme **alone** could achieve the desired result, and thus the solubilization and extraction steps could be omitted. There is nothing in either Hart *et al.* or in Wetzel *et al.* suggesting that coexpression should be performed using certain types of promoters, and by inducing the expression of the phage lysozyme only after about 50% or more of the heterologous protein has accumulated. Finally, there is no teaching or suggestion in either Hart *et al.* or Wetzel *et al.* to perform each step of the process in the absence of chloroform.

The rejection is based on impermissible hindsight reconstruction of the claimed invention

The requirement that an Examiner must show a suggestion to combine references cited in support of an obviousness rejection is a critical safeguard against hindsight reconstruction of an invention. In the foregoing arguments, Applicants have demonstrated that the Examiner failed to show proper motivation for making the purported combination. It is only with hindsight reconstruction of the invention, using the disclosure of the present application, that the Examiner could have been led to the finding of obviousness over the cited combination of references. It is,

however, well established that it is impermissible to use the claimed invention as an instruction manual or "template" to piece together the teachings of prior art so that the claimed invention is rendered obvious.

Accordingly, the rejection of Claims 1-7 and 9-24 is believed to be misplaced and should be withdrawn.

2. Claim 8 was rejected under 35 U.S.C. §103(a) as "being unpatentable" over Hart *et al.* in view of Wetzel *et al.* "as applied to the claims above," and further in view of Wick *et al.*, Infect. Immun. 1993, Nov., 61(11):4848-56. Wick *et al.* was cited for its teaching of nucleic acid encoding the lamB signal sequence for expression in the periplasm of *E. coli*.

As explained in response to the previous rejection, the combination of Hart *et al.* and Wetzel *et al.* is improper and does not yield the claimed invention. Since Wick *et al.* does not cure the underlying discussed deficiencies of the primary references with respect to Claim 8, the present rejection should be withdrawn for the same reasons as the foregoing rejection of Claims 1-7 and 9-24.

3. Claim 25 was rejected under 35 U.S.C. §103(a) as "being unpatentable" over Hart *et al.* in view of Wetzel *et al.* "as applied to the claimed above," and further in view of Balbas *et al.* (Gene, 1996 June 12:172(1):65-9). Balbas *et al.* was cited for its teaching of the plasmid pBRINT, which is an efficient vector for chromosomal integration of clones DNA into the lacZ gene of *E. coli*, and of the method for such integration, and that the integration is advantageous with respect to stability or undesired copy number effects.

As explained in response to the previous rejection, the combination of Hart *et al.* and Wetzel *et al.* is improper and does not yield the claimed invention. Since Balbas *et al.* does not cure the discussed deficiencies of the primary references, the present rejection should be withdrawn for the same reasons as the foregoing rejection of Claims 1-7 and 9-24.

All claims pending in this application are believed to be in *prima facie* condition for allowance, and an early action to that effect is respectfully solicited. Should any of the current rejections be maintained, the Examiner is respectfully requested to contact the undersigned to arrange a telephonic or personal interview before issuing a further Office Action.

Please charge any additional fees, including any additional fees for extension of time, or credit overpayment to Deposit Account No. **08-1641** (Attorney's Docket No. **39766-0128 A**).

Please direct any calls in connection with this application to the undersigned at the number provided below.

Respectfully submitted,

Date: February 9, 2006

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2/9/06 3:18 PM (39766.0128)